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(54) Title: PYRAZOLE COMPOUNDS USEFUL AS PROTEIN KINASE INHIBITORS

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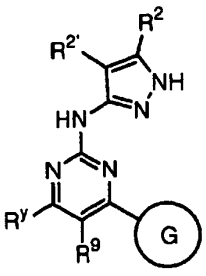
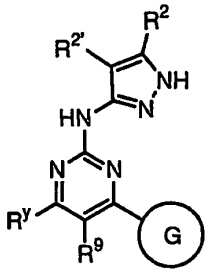


(VII)

(57) Abstract: This invention describes novel protein kinase inhibitors of formula (VII): wherein G is Ring C or Ring D; Ring C is selected from a phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, or 1,2,4-triazinyl ring, wherein said Rind C has one or two ortho substituents independently selected from -R^1; Ring D is a 5-7 membered monocyclic ring or 8-10 membered bicyclic ring selected from aryl, heteroaryl, heterocyclyl or carbocyclyl; R^y is T-R^{3*}; T is a valence bond or a C_{1-4} alkylidene chain; R^{3*} is an optionally substituted group selected from C_{1-6} alphatic, C_{3-10} carbocyclyl, C_{6-10} aryl, a heteroaryl ring having 5-10 ring atoms; and R^1, R^2, and $R^{2'}$ are as described in the specification. The protein kinase are useful for treating diseases such as cancer, diabetes and Alzheimer's disease.

We claim:

1. A compound of formula VII:



VII

or a pharmaceutically acceptable derivative or prodrug thereof, wherein:

G is Ring C or Ring D;

Ring C is selected from a phenyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, or 1,2,4-triazinyl ring, wherein said Ring C has one or two ortho substituents independently selected from $-R^1$, any non-ortho carbon position on Ring C is optionally and independently substituted by $-R^5$, and two adjacent substituents on Ring C are optionally taken together with their intervening atoms to form a fused, unsaturated or partially unsaturated, 5-6 membered ring having 0-3 heteroatoms selected from oxygen, sulfur or nitrogen, said fused ring being optionally substituted by halo, oxo, or $-R^8$;

Ring D is a 5-7 membered monocyclic ring or 8-10 membered bicyclic ring selected from aryl, heteroaryl, heterocyclyl or carbocyclyl, said heteroaryl or heterocyclyl ring having 1-4 ring heteroatoms selected from nitrogen, oxygen or sulfur, wherein Ring D is substituted at any substitutable ring carbon by oxo or $-R^5$, and at any substitutable ring nitrogen by $-R^4$, provided that when Ring D is a six-membered aryl or

heteroaryl ring, $-R^5$ is hydrogen at each ortho carbon position of Ring D;

R^1 is selected from -halo, -CN, $-NO_2$, T-V-R^6, phenyl, 5-6 membered heteroaryl ring, 5-6 membered heterocyclyl ring, or C_{1-6} aliphatic group, said phenyl, heteroaryl, and heterocyclyl rings each optionally substituted by up to three groups independently selected from halo, oxo, or $-R^8$, said C_{1-6} aliphatic group optionally substituted with halo, cyano, nitro, or oxygen, or R^1 and an adjacent substituent taken together with their intervening atoms form said ring fused to Ring C;

R^Y is hydrogen or T-$R^{3''}$;

T is a valence bond or a C_{1-4} alkylidene chain;

R^2 and $R^{2'}$ are independently selected from -R, -T-W-R^6, or R^2 and $R^{2'}$ are taken together with their intervening atoms to form a fused, 5-8 membered, unsaturated or partially unsaturated, ring having 0-3 ring heteroatoms selected from nitrogen, oxygen, or sulfur, wherein each substitutable carbon on said fused ring formed by R^2 and $R^{2'}$ is substituted by halo, oxo, -CN, $-NO_2$, $-R^7$, or -V-R^6, and any substitutable nitrogen on said ring formed by R^2 and $R^{2'}$ is substituted by R^4;

$R^{3''}$ is selected from an optionally substituted group selected from C_{3-10} carbocyclyl, C_{6-10} aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms;

each R is independently selected from hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, C_{6-10} aryl, a heteroaryl ring having 5-10 ring atoms, or a heterocyclyl ring having 5-10 ring atoms;

each R^4 is independently selected from $-R^7$, $-COR^7$, $-CO_2$(optionally substituted C_{1-6} aliphatic), $-CON(R^7)_2$, or $-SO_2R^7$, or two R^4 on the same nitrogen are taken

together to form a 5-8 membered heterocyclyl or heteroaryl ring;

each R^5 is independently selected from -R, halo, -OR, $-C(=O)R$, $-CO_2R$, -COCOR, $-NO_2$, -CN, $-S(O)R$, $-SO_2R$, -SR, $-N(R^4)_2$, $-CON(R^4)_2$, $-SO_2N(R^4)_2$, $-OC(=O)R$, $-N(R^4)COR$, $-N(R^4)CO_2$(optionally substituted C_{1-6} aliphatic), $-N(R^4)N(R^4)_2$, $-C=NN(R^4)_2$, -C=N-OR, $-N(R^4)CON(R^4)_2$, $-N(R^4)SO_2N(R^4)_2$, $-N(R^4)SO_2R$, or $-OC(=O)N(R^4)_2$, or R^5 and an adjacent substituent taken together with their intervening atoms form said ring fused to Ring C;

V is -O-, -S-, -SO-, $-SO_2-$, $-N(R^6)SO_2-$, $-SO_2N(R^6)-$, $-N(R^6)-$, -CO-, $-CO_2-$, $-N(R^6)CO-$, $-N(R^6)C(O)O-$, $-N(R^6)CON(R^6)-$, $-N(R^6)SO_2N(R^6)-$, $-N(R^6)N(R^6)-$, $-C(O)N(R^6)-$, $-OC(O)N(R^6)-$, $-C(R^6)_2O-$, $-C(R^6)_2S-$, $-C(R^6)_2SO-$, $-C(R^6)_2SO_2-$, $-C(R^6)_2SO_2N(R^6)-$, $-C(R^6)_2N(R^6)-$, $-C(R^6)_2N(R^6)C(O)-$, $-C(R^6)_2N(R^6)C(O)O-$, $-C(R^6)=NN(R^6)-$, $-C(R^6)=N-O-$, $-C(R^6)_2N(R^6)N(R^6)-$, $-C(R^6)_2N(R^6)SO_2N(R^6)-$, or $-C(R^6)_2N(R^6)CON(R^6)-$;

W is $-C(R^6)_2O-$, $-C(R^6)_2S-$, $-C(R^6)_2SO-$, $-C(R^6)_2SO_2-$, $-C(R^6)_2SO_2N(R^6)-$, $-C(R^6)_2N(R^6)-$, -CO-, $-CO_2-$, $-C(R^6)OC(O)-$, $-C(R^6)OC(O)N(R^6)-$, $-C(R^6)_2N(R^6)CO-$, $-C(R^6)_2N(R^6)C(O)O-$, $-C(R^6)=NN(R^6)-$, $-C(R^6)=N-O-$, $-C(R^6)_2N(R^6)N(R^6)-$, $-C(R^6)_2N(R^6)SO_2N(R^6)-$, $-C(R^6)_2N(R^6)CON(R^6)-$, or $-CON(R^6)-$;

each R^6 is independently selected from hydrogen, an optionally substituted C_{1-4} aliphatic group, or two R^6 groups on the same nitrogen atom are taken together with the nitrogen atom to form a 5-6 membered heterocyclyl or heteroaryl ring;

each R^7 is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic group, or two R^7 on the same nitrogen are taken together with the nitrogen to form a 5-8 membered heterocyclyl or heteroaryl ring;

each R^8 is independently selected from an optionally substituted C_{1-4} aliphatic group, $-OR^6$, $-SR^6$, $-COR^6$, $-SO_2R^6$, $-N(R^6)_2$, $-N(R^6)N(R^6)_2$, $-CN$, $-NO_2$, $-CON(R^6)_2$, or $-CO_2R^6$; and

R^9 is selected from -R, halo, -OR, $-C(=O)R$, $-CO_2R$, -COCOR, $-NO_2$, -CN, $-S(O)R$, $-SO_2R$, -SR, $-N(R^4)_2$, $-CON(R^4)_2$, $-SO_2N(R^4)_2$, $-OC(=O)R$, $-N(R^4)COR$, $-N(R^4)CO_2$(optionally substituted C_{1-6} aliphatic), $-N(R^4)N(R^4)_2$, $-C=NN(R^4)_2$, $-C=N-OR$, $-N(R^4)CON(R^4)_2$, $-N(R^4)SO_2N(R^4)_2$, $-N(R^4)SO_2R$, or $-OC(=O)N(R^4)_2$.

2. The compound according to claim 1, wherein said compound has one or more features selected from the group consisting of:

(a) Ring C is an optionally substituted ring selected from phenyl or pyridinyl, wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is selected from a naphthyl, quinolinyl or isoquinolinyl ring, and R^1 is -halo, an optionally substituted C_{1-6} aliphatic group, phenyl, $-COR^6$, $-OR^6$, -CN, $-SO_2R^6$, $-SO_2NH_2$, $-N(R^6)_2$, $-CO_2R^6$, $-CONH_2$, $-NHCOR^6$, $-OC(O)NH_2$, or $-NHSO_2R^6$; or Ring D is an optionally substituted ring selected from a phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, azepanyl, morpholinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydro-1*H*-isoindolyl, 2,3-dihydro-1*H*-indolyl, isoquinolinyl, quinolinyl, or naphthyl ring;

(b) R^Y is $T-R^{3''}$, wherein T is a valence bond or a methylene; and

(c) $R^{2'}$ is hydrogen and R^2 is hydrogen or a substituted or unsubstituted group selected from aryl, heteroaryl, or a C_{1-6} aliphatic group, or R^2 and $R^{2'}$ are taken together with their intervening atoms to form a

substituted or unsubstituted benzo, pyrido, pyrimido or partially unsaturated 6-membered carbocyclo ring.

3. The compound according to claim 2, wherein:

(a) Ring C is an optionally substituted ring selected from phenyl or pyridinyl, wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is selected from a naphthyl, quinolinyl or isoquinolinyl ring, and R^1 is -halo, an optionally substituted C_{1-6} aliphatic group, phenyl, $-COR^6$, $-OR^6$, -CN, $-SO_2R^6$, $-SO_2NH_2$, $-N(R^6)_2$, $-CO_2R^6$, $-CONH_2$, $-NHCOR^6$, $-OC(O)NH_2$, or $-NHSO_2R^6$; or Ring D is an optionally substituted ring selected from a phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, thienyl, azepanyl, morpholinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydro-1*H*-isoindolyl, 2,3-dihydro-1*H*-indolyl, isoquinolinyl, quinolinyl, or naphthyl ring;

(b) R^Y is $T-R^{3''}$, wherein T is a valence bond or a methylene; and

(c) $R^{2'}$ is hydrogen and R^2 is hydrogen or a substituted or unsubstituted group selected from aryl, heteroaryl, or a C_{1-6} aliphatic group, or R^2 and $R^{2'}$ are taken together with their intervening atoms to form a substituted or unsubstituted benzo, pyrido, pyrimido or partially unsaturated 6-membered carbocyclo ring.

4. The compound according to claim 2, wherein said compound has one or more features selected from the group consisting of:

(a) Ring C is an optionally substituted ring selected from phenyl or pyridinyl, wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is a naphthyl ring,

and R^1 is -halo, a C_{1-6} haloaliphatic group, a C_{1-6} aliphatic group, phenyl, or -CN; or Ring D is an optionally substituted ring selected from phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 2,3-dihydro-1*H*-isoindolyl, 2,3-dihydro-1*H*-indolyl, isoquinolinyl, quinolinyl, or naphthyl;

(b) R^Y is $T\text{-}R^{3''}$, wherein T is a valence bond or a methylene and $R^{3''}$ is an optionally substituted group selected from C_{3-6} carbocyclyl, phenyl, or a 5-6 membered heteroaryl or heterocyclyl ring;

(c) $R^{2'}$ is hydrogen and R^2 is hydrogen or a substituted or unsubstituted group selected from aryl, or a C_{1-6} aliphatic group, or R^2 and $R^{2'}$ are taken together with their intervening atoms to form a substituted or unsubstituted benzo, pyrido, pyrimido or partially unsaturated 6-membered carbocyclo ring; and

(d) Ring D is substituted by oxo or R^5, wherein each R^5 is independently selected from -halo, -CN, $-NO_2$, $-N(R^4)_2$, optionally substituted C_{1-6} aliphatic group, -OR, $-C(O)R$, $-CO_2R$, $-CONH(R^4)$, $-N(R^4)COR$, $-SO_2N(R^4)_2$, or $-N(R^4)SO_2R$.

5. The compound according to claim 4, wherein:

(a) Ring C is a n optionally substituted ring selected from phenyl or pyridinyl, wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is a naphthyl ring, and R^1 is -halo, a C_{1-6} haloaliphatic group, a C_{1-6} aliphatic group, phenyl, or -CN; or Ring D is an optionally substituted ring selected from phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-

tetrahydroquinolinyl, 2,3-dihydro-1*H*-isoindolyl, 2,3-dihydro-1*H*-indolyl, isoquinolinyl, quinolinyl, or naphthyl;

(b) R^Y is T-$R^{3''}$, wherein T is a valence bond or a methylene and $R^{3''}$ is an optionally substituted group selected from C_{3-6} carbocyclyl, phenyl, or a 5-6 membered heteroaryl or heterocyclyl ring;

(c) $R^{2'}$ is hydrogen and R^2 is hydrogen or a substituted or unsubstituted group selected from aryl, or a C_{1-6} aliphatic group, or R^2 and $R^{2'}$ are taken together with their intervening atoms to form a substituted or unsubstituted benzo, pyrido, pyrimido or partially unsaturated 6-membered carbocyclo ring; and

(d) Ring D is substituted by oxo or R^5, wherein each R^5 is independently selected from -halo, -CN, $-NO_2$, $-N(R^4)_2$, optionally substituted C_{1-6} aliphatic group, -OR, $-C(O)R$, $-CO_2R$, $-CONH(R^4)$, $-N(R^4)COR$, $-SO_2N(R^4)_2$, or $-N(R^4)SO_2R$.

6. The compound according to claim 4, wherein said compound has one or more of the features selected from the group consisting of:

(a) R^Y is T-$R^{3''}$, wherein T is a valence bond or a methylene and $R^{3''}$ is an optionally substituted group selected from phenyl, or a 5-6 membered heteroaryl or heterocyclyl ring;

(b) Ring C is an optionally substituted ring selected from phenyl or pyridinyl, wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is a naphthyl ring, and R^1 is -halo, a C_{1-4} aliphatic group optionally substituted with halogen, or -CN; or Ring D is an optionally substituted ring selected from phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl,

morpholinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, isoquinolinyl, quinolinyl, or naphthyl;

(c) R^2 and $R^{2'}$ are taken together with their intervening atoms to form a benzo, pyrido, pyrimido or partially unsaturated 6-membered carbocyclo ring optionally substituted with -halo, $-N(R^4)_2$, $-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl, $-NO_2$, $-O(C_{1-4}$ alkyl), $-CO_2(C_{1-4}$ alkyl), -CN, $-SO_2(C_{1-4}$ alkyl), $-SO_2NH_2$, $-OC(O)NH_2$, $-NH_2SO_2(C_{1-4}$ alkyl), $-NHC(O)(C_{1-4}$ alkyl), $-C(O)NH_2$, or $-CO(C_{1-4}$ alkyl), wherein the (C_{1-4} alkyl) is a straight, branched, or cyclic alkyl group; and

(d) Ring D is substituted by oxo or R^5, wherein each R^5 is independently selected from -Cl, -F, -CN, $-CF_3$, $-NH_2$, $-NH(C_{1-4}$ aliphatic), $-N(C_{1-4}$ aliphatic)$_2$, $-O(C_{1-4}$ aliphatic), C_{1-4} aliphatic, and $-CO_2(C_{1-4}$ aliphatic).

7. The compound according to claim 6, wherein:

(a) R^Y is T-$R^{3''}$, wherein T is a valence bond or a methylene and $R^{3''}$ is an optionally substituted group selected from phenyl, or a 5-6 membered heteroaryl or heterocyclyl ring;

(b) Ring C is an optionally substituted ring selected from phenyl or pyridinyl, wherein when Ring C and two adjacent substituents thereon form a bicyclic ring system, the bicyclic ring system is a naphthyl ring, and R^1 is -halo, a C_{1-4} aliphatic group optionally substituted with halogen, or -CN; or Ring D is an optionally substituted ring selected from phenyl, pyridinyl, piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, isoquinolinyl, quinolinyl, or naphthyl;

(c) R^2 and $R^{2'}$ are taken together with their intervening atoms to form a benzo, pyrido, pyrimido or partially unsaturated 6-membered carbocyclo ring optionally substituted with -halo, $-N(R^4)_2$, $-C_{1-4}$ alkyl, $-C_{1-4}$ haloalkyl, $-NO_2$, $-O(C_{1-4}$ alkyl), $-CO_2(C_{1-4}$ alkyl), -CN, $-SO_2(C_{1-4}$ alkyl), $-SO_2NH_2$, $-OC(O)NH_2$, $-NH_2SO_2(C_{1-4}$ alkyl), $-NHC(O)(C_{1-4}$ alkyl), $-C(O)NH_2$, or $-CO(C_{1-4}$ alkyl), wherein the (C_{1-4} alkyl) is a straight, branched, or cyclic alkyl group; and

(d) Ring D is substituted by oxo or R^5, wherein each R^5 is independently selected from -Cl, -F, -CN, $-CF_3$, $-NH_2$, $-NH(C_{1-4}$ aliphatic), $-N(C_{1-4}$ aliphatic)$_2$, $-O(C_{1-4}$ aliphatic), C_{1-4} aliphatic, and $-CO_2(C_{1-4}$ aliphatic).

8. The compound according to claim 7, wherein said compound is selected from Table 6.

9. A composition comprising a compound according to any of claims 1-8 and a pharmaceutically acceptable carrier.

10. The composition according to claim 9 further comprising a second therapeutic agent.

11. A method of inhibiting GSK-3 or Aurora activity in a patient comprising the step of administering to said patient a therapeutically effective amount of the composition according to claim 9.

12. The method according to claim 11, wherein said method inhibits GSK-3 activity in a patient.

13. A method of inhibiting GSK-3 or Aurora activity in a biological sample comprising contacting said biological sample with the compound according to claim 1.

14. A method of treating a disease that is alleviated by treatment with an GSK-3 inhibitor, said method comprising the step of administering to a patient in need of such a treatment a therapeutically effective amount of the composition according to claim 9.

15. The method according to claim 14 further comprising the step of administering to said patient a second therapeutic agent.

16. The method according to claim 14, wherein said disease is diabetes.

17. The method according to claim 14, wherein said disease is Alzheimer's disease.

18. The method according to claim 14, wherein said disease is schizophrenia.

19. A method of enhancing glycogen synthesis in a patient in need thereof, which method comprises the step of administering to said patient a therapeutically effective amount of the composition according to claim 9.

20. A method of lowering blood levels of glucose in a patient in need thereof, which method comprises the step of administering to said patient a therapeutically effective amount of the composition according to claim 9.

21. A method of inhibiting the production of hyperphosphorylated Tau protein in a patient in need thereof, which method comprises the step of administering to said patient a therapeutically effective amount of the composition according to claim 9.

22. A method of inhibiting the phosphorylation of β-catenin in a patient in need thereof, which method comprises the step of administering to said patient a therapeutically effective amount of the composition according to claim 9.

23. A method of treating a disease that is alleviated by treatment with an aurora inhibitor, which method comprises the step of administering to a patient in need of such a treatment a therapeutically effective amount of the composition according to claim 9.

24. The method according to claim 23, further comprising the step of administering to said patient a second therapeutic agent.

25. The method according to claim 23 wherein said disease is cancer.

INTERNATIONAL SEARCH REPORT

Ir onal Application No
I /US 2152

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D403/12 C07D401/14 A61K31/506 A61K31/53 A61P35/00
C07D403/14 C07D405/14 C07D521/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
29 November 2001	10/12/2001

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Form PCT/ISA/210 (second sheet) (July 1992)

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